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Initiation of Psychotropic Drugs in Spouses of Patients With Early-Onset Alzheimer's Disease: A Matched Cohort Study

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ABSTRACT

Objectives: The diagnosis of early-onset Alzheimer's disease (EOAD) can cause emotional stress not only to the patients themselves but also to their spouses. This study aimed to evaluate the risk of psychiatric disorders in spouses of EOAD patients, using psychotropic drug initiation as a surrogate indicator.

Methods: A cohort study was conducted using a Japanese claims database, with spouses of EOAD patients (exposed spouses) matched with spouses of non-EOAD individuals (reference spouses) up to a 1:10 ratio. Primary outcome was the initiation of mood disorder drugs, and secondary outcomes were the initiation of drugs for anxiety disorders, sleep disorders, and schizophrenia spectrum disorders. Four study cohorts were created according to each outcome analysis. Multivariable Cox regression models were used to estimate adjusted hazard ratios (aHRs) and their 95% confidence intervals (CIs) for study outcomes.

Results: The analysis of mood disorder drugs included 395 exposed spouses and 3711 reference spouses. The proportion of patients excluded from the analysis due to prescription of mood disorder drugs during the baseline period was 4.3% higher among exposed spouses than reference spouses. There was no major difference between groups with respect to mood disorder drug initiation after 1 year (aHR, 2.08 [95% CI, 0.61 to 7.13]). In subgroup analysis of females and dependents, exposed spouses showed a higher rate of initiation (females: aHR, 6.39 [95% CI, 1.24 to 32.80]; dependents: aHR, 6.47 [95% CI, 1.25 to 33.55]). No substantial differences in secondary outcomes were observed in any comparison.

Conclusions: This study does not conclusively demonstrate an increase in mood disorder drug initiation among spouses of EOAD patients overall; however, initiation rates may be higher among female or dependent spouses. Our findings also suggest that exposed spouses experience significant psychological stress prior to their partners' EOAD diagnoses.

Toshiki Fukasawa, Kota Matsumoto, and Kotaro Sasaki contributed equally to this work as first authors.

Summary

- This study compared the risk of psychiatric disorders in spouses of patients with early-onset Alzheimer's disease (EOAD) with those of non-EOAD individuals, using psychotropic drug initiation as a proxy measure of psychiatric disorders.
- No substantial difference was observed in the initiation of psychotropic drugs between spouses of EOAD patients and those of non-EOAD individuals.
- Within subgroups of female spouses and dependents, a higher initiation rate of mood disorder drugs was observed among spouses of EOAD patients compared to those of non-EOAD individuals.

1 | Introduction

Early-onset Alzheimer's disease (EOAD) is generally defined as Alzheimer's disease (AD) that develops before age 65, and accounts for approximately 5.5% of all AD cases [1]. Unlike late-onset Alzheimer's disease (LOAD), EOAD often presents with atypical clinical features, with more pronounced effects on executive, visuospatial, and motor functions but less memory loss [2]. EOAD typically occurs during the most productive years of an individual's life, which include career advancement and family-building activities. Compared to LOAD patients, EOAD patients are therefore more likely to experience a sudden loss of independence in midlife, face anticipatory grief about the future, and have difficulty maintaining employment and meeting financial and family responsibilities [3].

The progressive decline in daily functioning among EOAD patients heightens their dependence on their spouses, forcing a redefinition of spousal identity and relationships. Spouses often become primary caregivers, and confront unique challenges such as managing dual caregiving responsibilities for the patient and children, navigating life disruptions, relationship problems, and financial difficulties [4]. Moreover, since dementia services are predominantly tailored for older adults [5], insufficient support for younger patients can exacerbate stress among these spouses.

These challenges may precipitate psychiatric disorders among spouses of EOAD patients. Indeed, an Australian cross-sectional study found that 50% of 36 spouses reported mild to severe depression, as assessed by questionnaire [6]. The markedly lower incidence of EOAD has limited research in this area, with most studies hindered by small samples, cross-sectional designs, and a lack of comparison groups; further, their primary focus was limited to depression [4]. This background points to the critical need for a larger, more comprehensive cohort study.

This cohort study, the largest in this field to date, aimed to compare the risk of psychiatric disorders, including mood, anxiety, sleep, and schizophrenia spectrum disorders, between spouses of EOAD patients and those of non-EOAD individuals, using psychotropic drug initiation as a proxy measure for the development of psychiatric disorders.

2 | Materials and Methods

2.1 | Data Source

We used a Japanese health insurance claims database developed by JMDC Inc. [7, 8]. As of March 2023, this database contained records for 16 million working-age individuals and their family members, all aged under 75 years, enrolled in corporate health insurance societies. Typically, the head of the household, as the insured individual, can enroll family members as dependents to receive the same health insurance coverage, provided the dependents meet certain criteria, such as having a low income (< ¥1.3 million or approximately $8400 per year). The database provides longitudinal, individual-level information on demographics; insured/dependent status; diagnoses; and all reimbursed services, which include medical procedures and pharmacy dispensing. For specific individuals, health checkup data, including body mass index (BMI) and lifestyle behavior questionnaires are available [9]. The database enables tracking of healthcare resource consumption by insured individuals and their dependents, unless they withdraw from their health insurance society; withdrawal by insured individuals also results in the automatic withdrawal of their dependents. This database has been extensively used in clinical epidemiological studies [10, 11]. In the present study, we used data spanning from January 1, 2005, to June 30, 2023. The study protocol was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (approval number: R3912-1). Informed consent was not required due to the retrospective and anonymized nature of this study.

2.2 | Study Design, Study Population, and Exposure

We conducted a population-based matched cohort study comparing the spouses of EOAD patients with spouses of non-EOAD individuals. Exposure was defined as having a spouse diagnosed with EOAD, characterized as an AD diagnosis between ages 18 and 64, followed by a first prescription for an anti-dementia drug within 60 days of diagnosis. This approach was used to reduce misclassification that can occur when exposure is defined solely by International Classification of Diseases, Tenth Revision (ICD-10) codes, given the challenges in accurately diagnosing EOAD. Using information on prescriptions for anti-dementia drugs after the diagnosis introduces selection bias; however, given the short duration of 60 days, the introduced bias would be minimal. Cohort entry date for exposed spouses was the date of initial AD diagnosis in their EOAD partner, and was required to be between October 1, 2012 (183 days after April 1, 2012), and June 30, 2021 (2 years prior to June 30, 2023). This inclusion period was established based on three considerations: (1) claims data for dates prior to April 1, 2012 included the month only, not the specific day [12]; (2) continuous enrollment in the database for at least 180 days, as described below; and (3) a

maximum follow-up period of 2 years. Without consideration (1), if the exposure and outcome occurred within the same month, it would be impossible to determine which event occurred first, and outcomes that actually preceded the exposure could be mistakenly counted as exposure-related events. Spouses of patients who had a claim for mild cognitive impairment (MCI) at cohort entry or for non-AD dementia before or at cohort entry were excluded. Both EOAD patients and their spouses were required to have been continuously enrolled in the database for at least 180 days before cohort entry to increase the likelihood of identifying a first AD diagnosis and to collect baseline covariate data. Exposed spouses with MCI, dementia, or prescriptions for anti-dementia drugs prior to cohort entry were excluded. We created four cohorts to assess the initiation of drugs for mood disorders, anxiety disorders, sleep disorders, and schizophrenia spectrum disorders, excluding exposed spouses who had already been prescribed a respective drug of interest prior to cohort entry. For instance, in the cohort assessing mood disorder drug initiation, exposed spouses who had received a mood disorder drug at baseline were excluded, while those prescribed other psychotropic drugs were not.

Each exposed spouse was risk-set matched with up to 10 reference spouses of non-EOAD individuals from the database, based on couples' age, sex, insured/dependent status, and spouses' number of outpatient visits in the 180 days before cohort entry [13]. Reference spouses could be included multiple times across different matches [14]. To minimize selection bias due to differential loss to follow-up [15], continuous enrollment in the database until the first prescription of an anti-dementia drug for the corresponding EOAD patient was required for reference spouses. The same eligibility criteria applied to the reference spouses, except for their exposure status. Details of the inclusion and exclusion criteria can be found in Figure 1 and Supporting Information S1: Tables S1–S4 [16, 17].

2.3 | Study Outcomes and Follow-Up

The primary outcome was the incidence of initiation of mood disorder drugs 1 year post-cohort entry. Secondary outcomes similarly included the incidence of initiating drugs for anxiety disorders, sleep disorders, and schizophrenia spectrum disorders. These outcomes were also assessed at 2 years post-cohort entry. Given the documented inaccuracies of defining psychiatric disorders solely by ICD-10 codes [18], psychotropic drug prescriptions were used as a proxy for these disorders. These outcomes were defined by a combination of medical claims with an ICD-10 code for psychiatric disorders and the corresponding

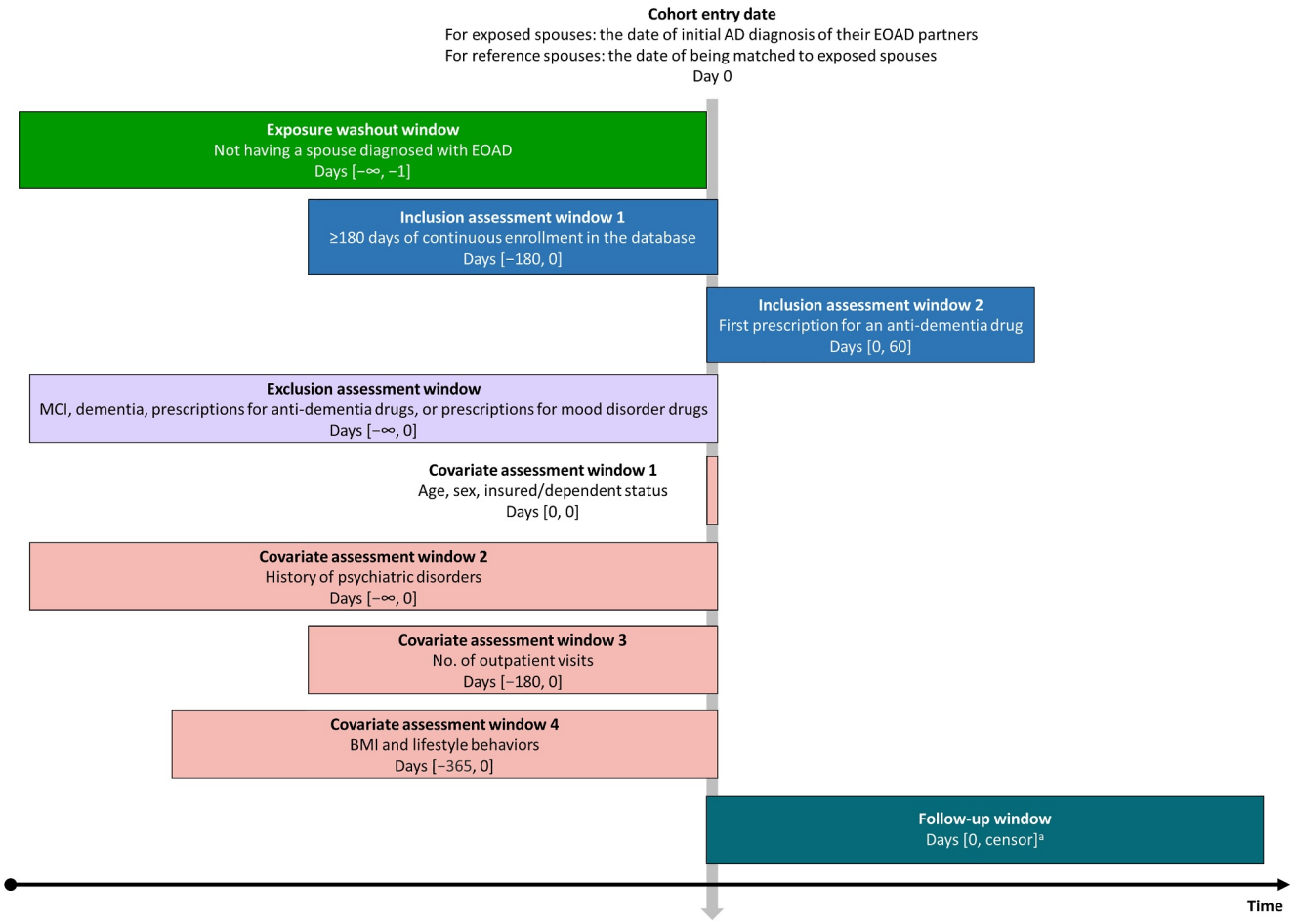

FIGURE 1 | Study design diagram. AD, Alzheimer's disease; BMI, body mass index; EOAD, early-onset Alzheimer's disease; MCI, mild cognitive impairment. [a]Study cohorts were followed for up to 2 years from cohort entry until the occurrence of an outcome, death, disenrollment from health insurance, or end of the study period (June 30, 2023), whichever came first.

psychotropic drug prescription for at least a 2-day supply (Supporting Information S1: Table S5).

Study cohorts were followed for up to 2 years from cohort entry until the occurrence of an outcome, death, disenrollment from health insurance, or the end of the study period (June 30, 2023), whichever came first. Although reference spouses could have become exposed after cohort entry, they were not excluded from follow-up since such exposure was anticipated to be very rare, occurring in only 0.08%–0.22% of each cohort.

2.4 | Covariates

We assessed the characteristics of the study population during the baseline period prior to cohort entry. Based on domain knowledge, the selected covariates included: (i) demographics (age, sex, insured/dependent status); (ii) history of psychiatric disorders (mood, anxiety, sleep, schizophrenia spectrum disorders); (iii) number of outpatient visits, used as a proxy for the intensity of care, overall disease state, and level of surveillance; (iv) BMI; and (v) lifestyle behaviors (smoking status, breakfast skipping, frequency of drinking alcohol, adequate sleep, exercise habits) (Supporting Information S1: Table S6) [13].

2.5 | Statistical Analysis

Covariate imbalance among comparison groups was evaluated using standardized mean differences (SMDs), with values greater than 0.2 considered significant. Crude incidence rates for study outcomes were estimated using the exact Poisson method [19]. Adjusted incidence rate differences (aIRDs) and adjusted hazard ratios (aHRs) were estimated using additive hazard models and Cox regression models, respectively [20]. The 95% confidence intervals (CIs) were calculated using cluster-robust variance estimators. Furthermore, we estimated the direct adjusted cumulative incidence curves using Cox regression models [21, 22]. The multivariable regression models adjusted for couples' ages and sex, the spouses' history of psychiatric disorders, and the number of outpatient visits. Among matching factors, we did not use insured/dependent status as an explanatory variable due to its strong correlation with sex. BMI and lifestyle behaviors were not included as explanatory variables in the models due to missing data for some or most participants. Instead, these data from subsets of participants were used to assess the balance among comparison groups.

To assess heterogeneity in the association, we also performed prespecified subgroup analyses stratified by sex, insured/dependent status, and history of psychiatric disorders. The p value for interaction was obtained by including a product interaction term between the exposure and each characteristic in the specified models, with a threshold of less than 0.05 considered statistically significant.

R version 4.3.1 (R Foundation for Statistical Computing) was used to create Table 1, estimate the aIRDs, and generate the direct adjusted cumulative incidence curve, while SAS version 9.4 (SAS Institute Inc.) was employed for all other analyses.

3 | Results

3.1 | Baseline Characteristics of Study Cohorts

The four study cohorts, constructed based on the eligibility criteria for each outcome analysis (Figure 2 and Supporting Information S1: Figures S1–S3), included a mood disorder drug analysis cohort (395 exposed spouses, 3711 reference spouses [3705 non-duplicate reference spouses]); an anxiety disorder cohort (384 exposed spouses, 3600 reference spouses [3593 non-duplicate reference spouses]); a sleep disorder cohort (396 exposed spouses, 3745 reference spouses [3736 non-duplicate reference spouses]); and a schizophrenia spectrum disorder cohort (426 exposed spouses, 4014 reference spouses [3999 non-duplicate reference spouses]). The percentage of spouses excluded due to psychotropic drug prescriptions during the baseline period was higher in the exposed group than in the reference group, with 4.3% for mood disorders, 5.1% for anxiety disorders, 5.5% for sleep disorders, and 3.2% for schizophrenia spectrum disorders.

In the cohort analyzing mood disorder drugs (Table 1), mean age (standard deviation) of exposed and reference spouses at baseline was 57.4 years (6.7) and 57.4 years (6.5), respectively. More than half of both exposed and reference spouses were male (57.5% and 58.8%, respectively) and insured (58.5% and 59.1%, respectively). All characteristics demonstrated similar distributions between the exposed and reference groups. Baseline characteristics of the other study cohorts were similar to those of the cohort for the analysis of mood disorder drugs (Supporting Information S1: Tables S7–S9).

3.2 | Initiation Rate of Psychotropic Drugs

During the 1-year follow-up period, initiation of mood disorder drugs occurred in three spouses (crude incidence rate, 8.17 per 1000 person-years) in the exposed group compared to 14 spouses (crude incidence rate, 4.01 per 1000 person-years) in the reference group (Table 2). There were no major differences between the groups, with an aIRD of 4.36 (95% CI, −5.23 to 13.94) per 1000 person-years and an aHR of 2.08 (95% CI, 0.61–7.13). During the 2-year follow-up period, the initiation of mood disorder drugs occurred in four spouses (crude incidence rate, 6.00 per 1000 person-years) in the exposed group compared to 27 spouses (crude incidence rate, 4.10 per 1000 person-years) in the reference group (Table 2). There were no substantial differences between the groups, with an aIRD of 1.94 (95% CI, −4.24 to 8.12) per 1000 person-years and an aHR of 1.45 (95% CI, 0.50–4.19). The time courses of the primary outcome are shown in Figure 3A.

For the initiation of drugs for anxiety disorders and sleep disorders, no clear differences were observed between groups at both 1 year (aHR, 0.89 [95% CI, 0.28 to 2.88] for anxiety disorders; 0.93 [95% CI, 0.32 to 2.66] for sleep disorders) and 2 years (aHR, 0.76 [95% CI, 0.28 to 2.09] for anxiety disorders; 1.09 [95% CI, 0.54 to 2.22] for sleep disorders) (Supporting Information S1: Tables S10 and S11). For the initiation of drugs for schizophrenia spectrum disorders, an aHR could not be obtained as no events occurred in the exposed group (Supporting Information S1:

TABLE 1 | Baseline characteristics of the cohort used to assess the initiation of drugs for mood disorders.

Baseline characteristic	Spouses of EOAD patients (n = 395)	Spouses of non-EOAD individuals (n = 3711)	SMD	EOAD patients (n = 395)	Non-EOAD individuals (n = 3711)	SMD
Age (years), mean (SD)	57.4 (6.7)	57.4 (6.5)	0.002	57.6 (5.7)	57.6 (5.8)	0.010
< 40 years	4 (1.0)	25 (0.7)	0.037	5 (1.3)	44 (1.2)	0.007
40–49 years	43 (10.9)	407 (11.0)	0.003	28 (7.1)	271 (7.3)	0.008
50–59 years	170 (43.0)	1641 (44.2)	0.024	175 (44.3)	1662 (44.8)	0.010
≥ 60 years	178 (45.1)	1638 (44.1)	0.019	187 (47.3)	1734 (46.7)	0.012
Male	227 (57.5)	2182 (58.8)	0.027	168 (42.5)	1529 (41.2)	0.027
Insured/dependent status						
Insured	231 (58.5)	2193 (59.1)	0.012	164 (41.5)	1518 (40.9)	0.012
Dependent	164 (41.5)	1518 (40.9)		231 (58.5)	2193 (59.1)	
History of psychiatric disorders						
Mood disorders	4 (1.0)	26 (0.7)	0.034	137 (34.7)	211 (5.7)	0.775
Anxiety disorders	23 (5.8)	120 (3.2)	0.125	157 (39.7)	360 (9.7)	0.743
Sleep disorders	31 (7.8)	232 (6.3)	0.062	132 (33.4)	469 (12.6)	0.509
Schizophrenia spectrum disorders	1 (0.3)	5 (0.1)	0.027	61 (15.4)	38 (1.0)	0.544
No. of outpatient visits, mean (SD)	4.4 (5.5)	3.8 (4.4)	0.129	10.7 (10.1)	5.2 (7.5)	0.617
BMI (kg/m^2), mean (SD)	23.2 (3.1)	23.5 (3.3)	0.096	22.4 (3.5)	23.1 (3.5)	0.184
< 18.5 kg/m^2	15 (3.8)	108 (2.9)	0.080	23 (5.8)	153 (4.1)	0.149
18.5 to < 25.0 kg/m^2	154 (39.0)	1543 (41.6)	0.003	127 (32.2)	1382 (37.2)	0.036
25.0 to < 30.0 kg/m^2	58 (14.7)	579 (15.6)	0.003	41 (10.4)	467 (12.6)	0.038
≥ 30 kg/m^2	4 (1.0)	89 (2.4)	0.128	5 (1.3)	76 (2.0)	0.064
Missing	164 (41.5)	1392 (37.5)	0.082	199 (50.4)	1633 (44.0)	0.128
Smoking						
Yes	61 (15.4)	536 (14.4)	0.078	39 (9.9)	421 (11.3)	0.013
No	165 (41.8)	1736 (46.8)	0.078	155 (39.2)	1619 (43.6)	0.013
Missing	169 (42.8)	1439 (38.8)	0.082	201 (50.9)	1671 (45.0)	0.117
Breakfast skipping						
Yes	33 (8.4)	249 (6.7)	0.124	25 (6.3)	197 (5.3)	0.101
No	173 (43.8)	1873 (50.5)	0.124	157 (39.7)	1690 (45.5)	0.101
Missing	189 (47.8)	1589 (42.8)	0.101	213 (53.9)	1824 (49.2)	0.096
Frequency of drinking alcohol						
Everyday	70 (17.7)	778 (21.0)	0.057	48 (12.2)	601 (16.2)	0.121
Occasional	61 (15.4)	700 (18.9)	0.074	52 (13.2)	543 (14.6)	0.006
Rare	78 (19.7)	670 (18.1)	0.129	85 (21.5)	770 (20.7)	0.116
Missing	186 (47.1)	1563 (42.1)	0.100	210 (53.2)	1797 (48.4)	0.095
Adequate sleep						
Yes	135 (34.2)	1461 (39.4)	0.061	132 (33.4)	1258 (33.9)	0.148
No	69 (17.5)	655 (17.7)	0.061	47 (11.9)	620 (16.7)	0.148
Missing	191 (48.4)	1595 (43.0)	0.108	216 (54.7)	1833 (49.4)	0.106

(Continues)

TABLE 1 | (Continued)

Baseline characteristic	Spouses of EOAD patients (n = 395)	Spouses of non-EOAD individuals (n = 3711)	SMD	EOAD patients (n = 395)	Non-EOAD individuals (n = 3711)	SMD
Exercise habits						
Yes	52 (13.2)	669 (18.0)	0.130	51 (12.9)	567 (15.3)	0.038
No	150 (38.0)	1446 (39.0)	0.130	128 (32.4)	1309 (35.3)	0.038
Missing	193 (48.9)	1596 (43.0)	0.118	216 (54.7)	1835 (49.4)	0.105

Note: Data are presented as number (percentage) of individuals unless otherwise indicated.
Abbreviations: BMI, body mass index; EOAD, early-onset Alzheimer's disease; SD, standard deviation; SMD, standardized mean difference.

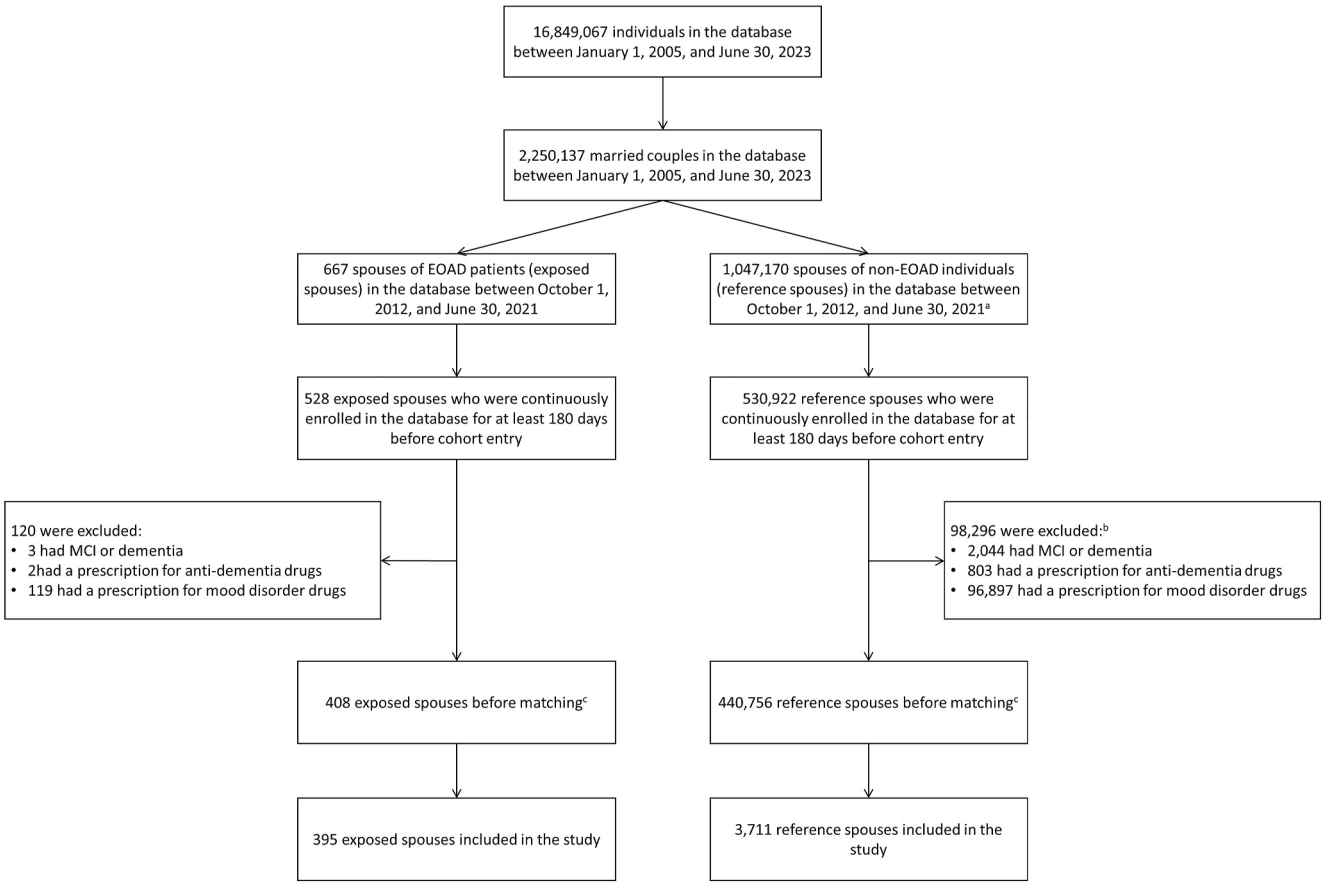

FIGURE 2 | Flow diagram of the cohort study assessing mood disorder drug initiation. EOAD, early-onset Alzheimer's disease; MCI, mild cognitive impairment. [a]After excluding exposed spouses who did not meet the exclusion criteria, risk-set sampling was performed based on couples' ages, sex, and insured/dependent status. [b]Because of the sampling with replacement in the reference group, this number does not match the difference observed before and after the exclusion. [c]Each exposed spouse was risk-set matched with up to 10 reference spouses of non-EOAD individuals from the database, based on couples' ages, sex, insured/dependent status, and spouses' number of outpatient visits in 180 days before cohort entry.

Table S12). The time courses of the secondary outcomes are shown in Figure 3B–D.

3.3 | Subgroup Analyses

For the initiation of mood disorder drugs at the 1-year follow-up, heterogeneity was evident when stratified by sex and insured/dependent status. Specifically, for females, the aHR was 6.39 (95% CI, 1.24–32.80). However, the aHR for males and the p value for multiplicative interaction could not be calculated due to the absence of events in the exposed group. The aIRD was 17.00 (95% CI, −5.99 to 40.00) for females and −4.40 (95% CI, −7.16 to −1.63) for males; the p value for additive interaction was 0.063 (Table 2). For dependents, the aHR was 6.47 (95% CI, 1.25–33.55). The aHR for insured individuals and the p value for multiplicative interaction could not be computed due to the absence of events in the

TABLE 2 | Incidence rates, adjusted incidence rate differences, and adjusted hazard ratios for initiation of mood disorder drugs.

	Spouses of EOAD patients		Spouses of non-EOAD individuals					
	No.	IR[a] (no. of events)	No.	IR[a] (no. of events)	aIRD[a,b] (95% CI)	*p*[c]	aHR[b] (95% CI)	*p*[d]
1-Year								
Main analysis	395	8.17 (3)	3711	4.01 (14)	4.36 (−5.23 to 13.94)	NA	2.08 (0.61–7.13)	NA
Subgroup analyses								
Sex						0.063		NA
Male	227	0.00 (0)	2182	4.87 (10)	−4.40 (−7.16 to −1.63)		NA	
Female	168	19.98 (3)	1529	2.78 (4)	17.00 (−5.99 to 40.00)		6.39 (1.24–32.80)	
Insured/dependent status						0.065		NA
Insured	231	0.00 (0)	2193	4.85 (10)	−4.32 (−7.07 to −1.56)		NA	
Dependent	164	20.53 (3)	1518	2.80 (4)	17.47 (−6.13 to 41.08)		6.47 (1.25–33.55)	
History of psychiatric disorders						0.679		0.787
Yes	49	22.90 (1)	336	13.01 (4)	9.89 (−35.07 to 54.84)		2.10 (0.26–17.00)	
No	346	6.18 (2)	3375	3.14 (10)	3.20 (−5.73 to 12.12)		2.05 (0.43–9.73)	
2-Year								
Main analysis	395	6.00 (4)	3711	4.10 (27)	1.94 (−4.24 to 8.12)	NA	1.45 (0.50–4.19)	NA
Subgroup analyses								
Sex						0.195		0.184
Male	227	2.44 (1)	2182	4.37 (17)	−1.66 (−6.86 to 3.53)		0.58 (0.08–4.38)	
Female	168	11.66 (3)	1529	3.71 (10)	7.91 (−5.50 to 21.32)		3.01 (0.81–11.08)	
Insured/dependent status						0.192		0.179
Insured	231	2.41 (1)	2193	4.35 (17)	−1.62 (−6.74 to 3.51)		0.58 (0.08–4.38)	
Dependent	164	11.96 (3)	1518	3.74 (10)	8.16 (−5.59 to 21.91)		3.05 (0.82–11.28)	
History of psychiatric disorders						0.891		0.902
Yes	49	12.71 (1)	336	10.49 (6)	2.96 (−22.37 to 28.30)		1.37 (0.15–12.75)	
No	346	5.10 (3)	3375	3.49 (21)	1.75 (−4.32 to 7.82)		1.51 (0.44–5.18)	

Abbreviations: aHR, adjusted hazard ratios; aIRD, adjusted incidence rate difference; CI, confidence interval; EOAD, early-onset Alzheimer's disease; IR, incidence rate; NA, not available.

[a]Per 1000 person-years.

[b]The multivariable regression models adjusted for couples' ages and sex, the spouses' history of psychiatric disorders, and the number of outpatient visits.

[c]*p* value for additive interaction.

[d]*p* value for multiplicative interaction.

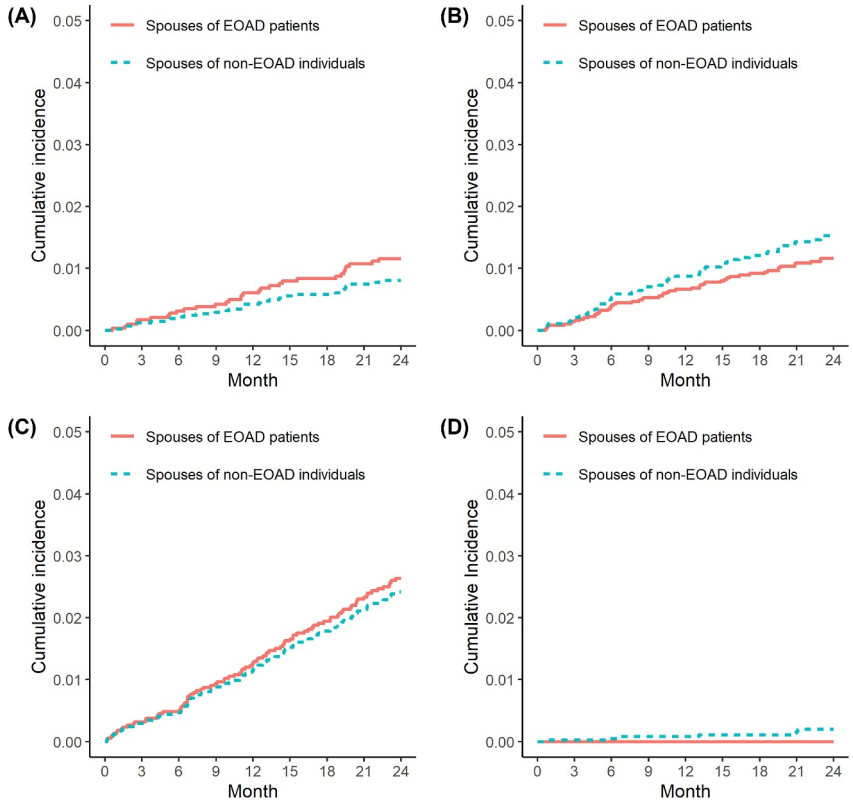

FIGURE 3 | Adjusted cumulative incidence of the initiation of drugs for (A) mood disorders, (B) anxiety disorders, (C) sleep disorders, and (D) schizophrenia spectrum disorders. EOAD, early-onset Alzheimer's disease. Panel (D) was created using the Kaplan–Meier method because the adjusted cumulative incidence curve could not be estimated with a Cox regression model due to the absence of events among spouses of EOAD patients.

exposed group. The aIRD was 17.47 (95% CI, −6.13 to 41.08) for dependents and −4.32 (95% CI, −7.07 to −1.56) for insured individuals; the *p* value for additive interaction was 0.065. No further evidence of heterogeneity was observed in the initiation of psychotropic drugs associated with exposure across other subgroups (Table 2 and Supporting Information S1: Tables S11–S13).

4 | Discussion

In this matched cohort study, we observed no clear differences in the initiation rate of psychotropic drugs between exposed spouses of EOAD patients and reference spouses of non-EOAD individuals after 1 year of follow-up. However, subgroup analyses revealed that female and dependent exposed spouses exhibited higher initiation rates of mood disorder drugs compared to their reference counterparts. Additionally, our study found that exposed spouses used more psychotropic drugs prior to their partner's EOAD diagnoses. This suggests that these spouses may have been experiencing higher levels of stress or underlying mental health issues even before the diagnosis, potentially due to the anticipatory stress associated with their partners' declining health. These findings emphasize the need for targeted mental health support for vulnerable spouses not only after the diagnosis but also during the period leading up to it.

Although the main analysis revealed no major differences between spouses with and without EOAD, we observed a trend toward higher rates of mood disorder drug initiation among spouses of EOAD patients. This trend is supported by an Australian cross-sectional study in which 50% of such spouses reported mild to severe depression [6]. However, the estimates in our present study might underestimate the true impact on spouses of EOAD patients for four reasons, warranting a cautious interpretation of the results. First, there is a cultural reluctance in Japan to use psychiatric labels, particularly for mild disorders, which can result in underreporting as individuals may not seek medical attention for conditions such as depression [23]. Second, due to the questionable validity of defining mood disorders solely by ICD-10 code [18], this study defined the outcome using a combination of these codes and corresponding drug prescriptions. However, a US cross-sectional study found that while 40% of AD caregivers were depressed, only 25.6% were on antidepressants [24]. Thus, while our results may primarily reflect moderate to severe mood disorders that require pharmacotherapy, they are unlikely to capture mild disorders. Third, this study did not consider the impact on spouses prior to their partners' EOAD diagnoses, as it excluded individuals who experienced relevant outcomes before cohort entry from the analysis. The proportion of subjects excluded due to prior prescriptions for mood disorder drugs was 4.3% higher in the exposed group than in the reference group, suggesting selection bias due to differential depletion of susceptibles. Given that dementia often manifests a lag of months to years between the onset of clinical symptoms and diagnosis [25, 26], the psychological burden on spouses prior to their partners' EOAD diagnoses can be substantial. In light of the

second and third points above, future research should reevaluate mood disorders before and after EOAD diagnosis through structured diagnostic interviews and questionnaires. Fourth, as the study subjects were covered by health insurance societies organized by large companies, they likely had higher income and education levels than the general population, potentially reducing their susceptibility to mood disorders [27]. This selection may limit the generalizability of our findings to couples who are covered by other Japanese health insurance schemes.

A subgroup analysis of females and dependents revealed a higher initiation rate of mood disorder drugs in the exposed group after 1 year of follow-up. In the analyzed population, the correlation between female and dependent subgroups was so strong ($r = 0.99$) that they were nearly identical. Although several reports indicate that female caregivers of early-onset dementia (EOD) patients experience more depression and adverse psychological effects than their male counterparts [4, 6, 28], this study could not separately analyze the impacts on females and dependents, constrained by the Japanese social structure and our target population. Given that unemployment rates are higher among individuals with EOD than those without [29], spouses of EOAD patients are likely to experience significant psychological stress from financial difficulties [4], particularly when the insured individual responsible for household income is diagnosed with EOAD. At the 2-year follow-up, the differences between groups had narrowed, but this may be due to selection bias due to loss to follow-up. Specifically, individuals with severe EOAD who require intensive nursing care may have been more likely to withdraw from the health insurance society early, thereby obscuring true associations over a longer follow-up period. This attrition could lead to an underestimation of heterogeneity, as the remaining sample may not adequately represent those with greater caregiving burdens. Considering the prevalent focus on dementia-related services for the elderly [5], there is a clear need to develop tailored support and services for younger patients and their families, who are often overlooked.

With regard to secondary outcomes, in addition to the same biases as for primary outcomes, some caution is needed in interpreting the results. The results for anxiety disorder drugs might have been underestimated if only mood disorder drugs were prescribed, given that anxiety disorders and depression often coexist, and affect over half of the patients [30]. Regarding sleep disorder drugs, spouses might intentionally avoid them to monitor the nighttime activities of EOAD patients [31], potentially leading to an underestimation of their use in the exposed group. In schizophrenia, new onset typically peaks in the early twenties for males and a few years later for females, followed by a decline in incidence for both sexes, with a smaller secondary peak for females in their mid-forties [32]. The mean age of the cohort studied for schizophrenia spectrum disorders was 57.5 years, and only 0.9% of participants were younger than 40 and only 11.9% were younger than 49, indicating that our study likely targeted a population at low risk for these disorders. Furthermore, meta-analyses of twin studies on schizophrenia indicate a significant genetic component [33], likely differing from those associated with other psychiatric disorders examined in this study.

Our study has four limitations. First, assessing exposure and outcomes based on claims data may have introduced information bias due to potential misclassification of these variables. However, by defining exposure and outcomes using a combination of ICD-10 codes and corresponding drug prescriptions, we likely minimized the risk of misclassification, on the expectation of a high positive predictive value for these variables. Second, residual confounding may have affected the results due to insufficient information about the couples' relationships and the socioeconomic status of the households. Third, the database characteristically limited enrollees to individuals with spouses registered as dependents, predominantly reflecting a subset of low-income spouses in Japan. This selection may restrict the generalizability of our findings to couples where spouses are not registered as dependents, namely those who do not fall into the low-income category [34]. Finally, although the study used a database of approximately 16 million individuals, this constitutes a relatively small sample size, albeit one of the largest when compared to previous studies. However, given that prospective studies require considerable time for subject recruitment and may not be feasible, use of a claims database is a promising alternative. Acknowledging the limited precision of our estimates, the accumulation of more data from additional cohort studies will yield more precise pooled estimates, and thereby improve confidence in our conclusions [35].

5 | Conclusion

This cohort study of matched spouses does not conclusively demonstrate an increase in mood disorder drug initiation among spouses of EOAD patients overall; however, initiation rates may be higher in female or dependent spouses. Our findings also indicate that exposed spouses had higher usage of psychotropic drugs prior to their partner's EOAD diagnosis. Spouses of EOAD patients continue to be an overlooked group within the policy and practice priorities of mental health services. Our study enhances understanding of psychiatric disorders in spouses of EOAD patients and highlights the need for comprehensive preventive care for mental health, particularly for the most vulnerable individuals.

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Conflicts of Interest

Toshiki Fukasawa has been employed by the Department of Digital Health and Epidemiology with support from Eisai Co., Ltd., Kyowa Kirin Co., Ltd., and Real World Data Co., Ltd.; and has received consulting fees from Real World Data Co., Ltd. Kota Matsumoto, Kotaro Sasaki, Yuta Goto, Yusuke Sakamoto, Yuta Kamada, Mika Ishii have been employed by Eisai Co., Ltd. Sachiko Tanaka-Mizuno was employed by the Department of Digital Health and Epidemiology with support from Eisai Co., Ltd., Kyowa Kirin Co., Ltd., and Real World Data Co., Ltd.; and has received consulting fees from Real World Data Co., Ltd. Satomi Yoshida was employed by the Department of Digital Health and Epidemiology with support from Eisai Co., Ltd., Kyowa Kirin Co., Ltd., and Real World Data Co., Ltd. Kayoko Mizuno has been employed by the Department of Digital Health and Epidemiology with support from Eisai Co., Ltd., Kyowa Kirin Co., Ltd., and Real World Data Co., Ltd.

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Data Availability Statement

The data cannot be shared publicly due to the privacy policy of JMDC Inc.

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Supporting Information

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